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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/723,365	11/26/2003	Dirk van den Boom	SEQ-2073-UT	4199

47328 7590 12/05/2006

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EXAMINER	
WOOLWINE, SAMUEL C	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 12/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/723,365	BOOM ET AL.	
	Examiner	Art Unit	
	Samuel Woolwine	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-39 and 58-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-39 and 58-73* is/are rejected.

7)☒ Claim(s) *12 and 65* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/18/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Claims 12-39 and 58-73 are pending, claims 1-11 and 40-57 are cancelled. Applicants' amendments to the claims filed 9/8/2006 are acknowledged.

Claim Rejections - 35 USC § 112 – Response to arguments

The rejection of claims 12-39 and 58-73 under this section of the previous Office action have been withdrawn in view of Applicants' amended claims, which are now all directed to analysis of nucleic acids, and in view of Applicants' arguments on page 11 of the response, which arguments are found persuasive.

Claim Rejections - 35 USC § 102 – Response to arguments

The rejection of claims 13-22, 24, 58 and 69-73 under this section of the previous Office action have been withdrawn in view of Applicants' amendments.

Claim Rejections - 35 USC § 103 – Response to arguments

Applicant's arguments with respect to claims 12, 26-32, 34-39 and 59-64, rejected under this section of the previous Office action have been considered but are moot in view of the new ground(s) of rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir.

1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-39 and 58-73 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application No. 10/933611. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of both applications are drawn to methods of determining sequence variations comprising the steps of obtaining a target and reference molecules, cleaving in a specific manner the target and reference molecules (or simulating cleavage of the latter), analyzing the masses of the resulting fragments, comparing the two sets of data, determining a reduced set of sequence variation candidates, and thereby determining sequence variations in the target nucleic acid compared to the reference nucleic acid. Compare claim 4 of the instant application with claim 19 of application 10/933611. The only difference between the two is that where claim 4 of the instant application recites (in claim 1) "contacting the target biomolecule with one or more specific cleavage reagents", claim 19 of the '611 application recites (in claim 1) "fragmenting a target nucleic acid at a plurality of specific and predictable sites".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Double Patenting – Response to arguments

This provisional rejection is maintained, since no arguments have been presented and a terminal disclaimer has not been filed.

Claim Objections

Claims 12 and 65 are objected to because of the following informalities: it appears that step f in claim 12 should refer to the identified different fragments in step e (as opposed to step a). Similarly, step f in claim 65 should refer to step d (as opposed to step b). Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-22, 24, 26-32, 34-39 and 58-73 rejected under 35 U.S.C. 103(a) as being unpatentable over Zabeau et al (WO 00/66771) in view of Little et al (1997, reference A255 on the IDS submitted 4/18/2006).

With regard to claims 12, 29, 35, 59 and 65, Zabeau teaches a method comprising:

(a) cleaving the target nucleic acid molecule into fragments by contacting the target nucleic acid molecule with one or more specific cleavage reagents (see page 7, lines 13-21);

(b) cleaving or simulating cleavage of a reference nucleic acid molecule into fragments with the same cleavage reagent (see page 7, lines 13-21);

(c) determining mass signals of the fragments produced in (a) and (b) (see page 7, lines 13-21);

(d) determining differences in the mass signals between the fragments produced in (a) and (b) (see page 7, lines 13-21);

(e) identifying fragments that are different between the target nucleic acid and the reference nucleic acid (see page 7, lines 13-21; comparing the mass spectra of the target and reference sequences would necessarily identify fragments that are different between the two);

(g) determining a reduced set of sequence variation candidates from the differences in the mass signals and thereby determining sequence variations in the target compared to the reference biomolecule (see page 7, lines 13-21; the detection of a mass necessarily defines a reduced set of sequence variation candidates, i.e. the set of all possible sequences is reduced to the set of all possible sequences having that particular mass):

> "In one embodiment, the present invention is directed to methods for sequence analysis of one or more target nucleic acids for which a known reference nucleic acid sequence is available. In this method, one or more target nucleic acids are derived from one or more biological samples, and a reference nucleic acid are each subjected to complementary cleavage reactions, and the products of the cleavage reactions are analyzed by mass spectroscopic methods. The mass spectra of the one or more target nucleic acids are then compared with the mass spectra of the reference nucleic acid sequence, and the nucleotide sequence of the one or more target nucleic acids is deduced by systematic computational analysis." (page 7, lines 13-21)

Zabeau also teaches applying the method to *a plurality of nucleic acid molecules* (page 5, lines 10-15; an additional limitation in claims 29 and 59), *a mixture of nucleic acids* (page 5, lines 10-15; an additional limitation in claim 35) and *performing more than one specific cleavage reaction* (page 6, lines 20-27; an additional limitation in claim 35), and to *determining single nucleotide polymorphisms* (page 15, lines 1-5; an additional limitation in claims 59 and 65). Zabeau also teaches scoring sequence

variations (page 10, lines 14-24 and page 33 line 5 through page 34 line 23; an additional limitation in claims 29, 35 and 59).

With regard to claim 13, Zabeau teaches an example *wherein differences in output signals are manifested as missing signals and/or additional signals* ("disappearance and appearance of three peaks"; see page 19, lines 5-19 and table 1).

With regard to claim 14, Zabeau teaches *mass spectrometry* (see page 7, lines 13-21).

With regard to claims 15-17, Zabeau teaches *determining single nucleotide polymorphisms* (page 15, lines 1-5, see also page 16, lines 23-26) which are mutations as well as polymorphisms as well as substitutions.

With regard to claims 18-20, Zabeau teaches his method can be applied to detecting sequence variations in *Mycobacterium tuberculosis* (see page 36, lines 4-6), which is also a prokaryote as well as a bacterium.

With regard to claims 21, 22, 32, 60, 61, 66 and 67, Zabeau teaches G-specific T_1 ribonuclease, the A-specific U_2 ribonuclease, the A/U specific phyM ribonuclease, the U/C specific ribonuclease A, the C-specific chicken liver ribonuclease (RNaseCL3), and cusativin (page 9, lines 18-21).

With regard to claim 24, Zabeau teaches *genotyping* (page 5 lines 28-29 and see example 5).

With regard to claims 26-28, see page 47 line 11 through page 48 line 13. Zabeau detects alleles with frequencies ranging from 5-10% and contemplates lower (i.e. less than 5%) detection limits.

With regard to claims 30, 31 and 34, Zabeau teaches applying the cleaved nucleic acid molecules to an array, specifically the onto a Spectrochip™ (Sequenom Inc., San Diego, CA) for analysis by MALDI-TOF-MS (see page 43, lines 22-25). As evidenced by the enclosed specification sheet for the Spectrochip™, this comprises an array as defined in paragraph [0314] of the specification.

With regard to claim 36, Zabeau teaches analysis of nucleic acid from tumor samples (page 6 lines 5-7).

With regard to claims 37 and 64, Zabeau teaches using nucleic acids pooled from individuals for genomic sequence analysis (page 6 lines 7-10).

With regard to claims 38 and 39 regarding the percentage of a mixed sample of nucleic acids that contains a sequence variation, Zabeau teaches analysis of nucleic acid from tumor samples (page 6 lines 5-7). Zabeau also teaches, on page 47 line 11 through page 48 line 13, that his method detects alleles in mixed samples with frequencies ranging from 5-10% and contemplates lower (i.e. less than 5%) detection limits. Zabeau does not specifically teach the use of his method to detect a mutant allele in a mixed sample obtained from a tumor sample, wherein the mutant allele comprises a specific percentage.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to use the method taught by Zabeau to detect a sequence variation, as taught by Zabeau, wherein the frequency of the mutant allele in the sample was less than 5%. One would have been motivated to do so because Zabeau teaches that detection of allele frequencies of less than 5% is

desirable. In addition, Zabeau teaches on page 6, lines 4-7 that using his methods "such sequences or sequence variants can be analyzed even when present as a lesser species. This is a *useful quality for the analysis of clinical samples which are often genetically heterogeneous* because of the presence of both normal and diseased cells or in itself (e.g., *cancerous tissue*, viralquasi-species)" (emphasis added).

With regard to claim 58, Zabeau teaches modification to alter cleavage specificity (page 9, lines 1-10).

With regard to claims 62 and 68 Zabeau teaches a method in which the target molecules is "selected from the group consisting of a single stranded DNA, a double stranded DNA, a cDNA, a single stranded RNA, a double stranded RNA, a DNA/RNA hybrid, and a DNA/RNA mosaic nucleic acid" (page 7, lines 27-30).

With regard to claims 63 and 69, Zabeau teaches target nucleic acids produced by transcription (page 8, lines 9-26).

With regard to claim 70, Zabeau teaches genome-wide discovery and scoring of SNPs useful as markers in genetic linkage studies (page 5, lines 16-18). While Zabeau does not explicitly teach the use of DNA from a single individual, the instruction to use SNPs for linkage analysis provides an implicit teaching to use DNA from a single individual. Chapter 2144.01 states:

> " '[I]n considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom.' *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968)"

One of skill in the art would infer that Zabeau teaches using genomic DNA from an individual for SNP-based linkage analysis, because such an analysis would yield meaningless results if performed with genomic DNA pooled from multiple individuals.

With regard to claims 71-73, Zabeau teaches determining SNPs further comprising scoring heterozygosity (see page 50, example 5). Although Zabeau does not specificly state scoring homozygosity, there is an implicit teaching of such, especially since Zabeau states: "a single specific cleavage reaction may often suffice for both allele and **zygosity** identification" (emphasis added). One of skill in the art would reasonably infer zygosity refers to both homozygosity as well as heterozygosity. See MPEP 2144.01 for a discussion of implicit disclosure.

Zabeau does not teach *determining compomers corresponding to the identified different fragments that are compomer witnesses* (step f, claim 12; step e, claim 29; step f, claim 35; step 3, claim 59; step f, claim 65).

Little teaches *determining compomers corresponding to different fragments that are compomer witnesses* (page 546, last paragraph in column 1, continuing in column 2, and see figure 2 and table 1). A compomer is simply a nucleotide base composition (see paragraph [0107] of the instant specification). A compomer witness is a compomer whose mass differs by a value that is less than or equal to a sufficiently small mass difference from the actual mass of a particular fragment (see paragraph [0108] of the specification). Therefore, when Little measures the masses of the fragments (in this case, primer extension products), and from these masses deduces a specific allele of apolipoprotein E that is present, he determines a compomer (he correlates the observed

mass with a specific primer extension product, an thus necessarily also correlates the mass with a specific base composition, i.e. a compomer). Since this compomer has a predicted mass which differs by a value (which is neither explicitly defined in the specification nor recited in the claim and thus can be any value) that is less than or equal to a sufficiently small mass difference from the actual observed mass of the fragment, this compomer is also a witness compomer. Thus this limitation can be interpreted to be nothing more than inferring the sequence of a fragment of a nucleic acid based on its mass.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to infer the sequence of the nucleic acids based on their observed masses (as was done by Little) when practicing the method of Zabeau, in order to obtain the benefit of deriving sequence information for diagnostic purposes, such as the genotyping of apolipoprotein E performed by Little, who states: "Clearly apolipoprotein E is an important protein to follow in laboratory medicine" (last sentence, first paragraph of introduction, page 545).

Claims 23 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zabeau et al (WO 00/66771) in view of Little et al (1997, reference A255 on the IDS submitted 4/18/2006) as applied to claims 12-22, 24, 26-32, 34-39 and 58-73 above, and further in view of McCarthy et al (WO 97/03210).

The teachings of Zabeau and Little have been discussed above. These references do not teach using DNA glycosylase to cleave the nucleic acid.

McCarthy teaches a method of achieving base-specific cleavage by introducing a modified base that is a substrate for a DNA glycosylase, excising the modified base using the DNA glycosylase to generate abasic sites, cleaving the phosphate linkages at the abasic sites, and analyzing the cleavage products produced (see abstract). McCarthy does not teach analyzing the cleavage products using mass spectrometry.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to use the base-specific cleavage of nucleic acid with glycosylase as taught be McCarthy in the method of nucleic acid analysis taught by Zabeau, because this was an art recognized means for achieving base-specific cleavage of nucleic acid.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zabeau et al (WO 00/66771) in view of Little et al (1997, reference A255 on the IDS submitted 4/18/2006) as applied to claims 12-22, 24, 26-32, 34-39 and 58-73 above, and further in view of Muller et al (2000).

The teachings of Zabeau and Little have been discussed above. These references do not teach analysis of epigenetic changes in a nucleic acid.

Muller teaches the use of a mass-spectrometry-based method for analyzing the imprinting status of the *TSSC3* gene (see page 757, column 2, penultimate paragraph). Muller does not teach a method involving base-specific cleavage of a target nucleic acid (but rather a target-dependent primer extension, like Little).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to apply the method of Zabeau to the analysis of imprinting status as taught by Muller, because, as Muller states on page 757, 1st sentence of the *Introduction*, "Epigenetic alterations to gene function are important in tumorigenesis". Therefore, one would have been motivated to substitute Zabeau's method for the method of Muller to assess epigenetic changes, since both Muller's and Zabeau's methods were art-recognized equivalents for the purpose of identifying sequence variations in a target nucleic acid.

Conclusion

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 4/18/2006 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

scw

JEFFREY FREDMAN
PRIMARY EXAMINER
11/19/06